CORRESPONDENCE

Role of total lung stress on the progression of early COVID-19 pneumonia: collinearity and potential confounders

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We read with great interest the article by Coppola and colleagues on the potential role of total lung stress in the disease progression of coronavirus disease 2019 (COVID-19)-related pneumonia [1]. We thank the authors for their work and appreciate the time and effort involved in performing all measurements including the assessment of the esophageal pressure swing (ΔP_{eso}) in COVID-19 patients on non-invasive respiratory support. However, we have some comments on the statistical methods, calculation of total lung stress, and potential confounders.

The authors studied the effects of total lung stress in early COVID-19 pneumonia. The associations of various variables recorded at day 1 with patient outcome were evaluated based on univariate p values. Variables with p values < 0.05 were included in a multivariable regression model. This practice, though widespread in clinical publications, is highly susceptible to bias and not very sensitive to confounding effects, particularly in small sample size studies [2].

Three variables were selected by this method: total lung stress, ΔP_{eso} and FiO_2/PaO_2 ratio. The authors claim that only total lung stress was independently associated with outcome. Since ΔP_{eso} is part of the formula for total lung stress, there is reason to believe that these variables are highly correlated. As collinearity is problematic in (generalized) linear models, we think that the study could benefit from additional sensitivity analyses presenting the results of a logistic model considering the FiO_2/PaO_2 ratio and only one of the other two variables.

In addition, the calculation of the total lung stress is subject to several assumptions that call into question the close relationship to the study outcome. The total lung stress, i.e. the maximum tension in the lung parenchyma counteracting forces applied through tidal breathing, is clinically defined as endinspiratory transalveolar pressure ($P_{el(L)}$). $P_{el(L)}$ is the transpulmonary pressure in the absence of airflow (i.e. under static conditions). The total lung stress computed by Coppola et al. includes a dynamic component (i.e. $\Delta P_{aw} - \Delta P_{eso}$). This leads to an overestimation of the $P_{el(L)}$ [3]. Seven patients with negative outcome had "abdominal respiratory mechanics". Recruitment of the expiratory muscles rises end-expiratory esophageal pressure. This elevates the measured ΔP_{eso} which in turn could make the computed lung stress appear higher than it actually was.

The authors considered positive end-expiratory pressure (PEEP) to be mandatory included into the total lung stress formula. But a recent study showed a significant reduction in intubation rate with higher PEEP (continuous positive airway pressure) compared to low PEEP (nasal high flow) suggesting a rather protective effect of PEEP induced lung stress [4].

In our opinion, these points underline the importance of searching for unmeasured confounding. It seems conceivable that disease severity correlates with increased pulmonary vascular thrombosis and correspondingly increased physiological dead space [5]. This would increase the ventilatory equivalent for CO_2 and be associated with an increased ΔP_{eso}. It would, therefore, interesting to include d-dimers as surrogate parameter as well as other established confounders such as age, obesity or cardiovascular diseases in the analysis, though the potential

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for overly exhaustive exploratory analysis is limited by the given sample size.

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Declarations

Conflicts of interest
The authors declare to have no conflicts of interest.

Research involving human participants and/or animals
The study did not involve human or animals.

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